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Baker Donelson Bearman, Caldwell & Berkowitz, PC 555 Eleventh Street, NW, Sixth Floor Washington, DC 20004			STRZELECKA, TERESA E	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>
	10/075,593	HEATH ET AL.
	<b>Examiner</b> TERESA E. STRZELECKA	<b>Art Unit</b> 1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(e).

#### **Status**

1) Responsive to communication(s) filed on 01 December 2008.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### **Disposition of Claims**

4) Claim(s) 1-7,10-17,19-28,31-38,40-49,52-59 and 61-65 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-7,10-17,19-28,31-38,40-49,52-59 and 61-65 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### **Application Papers**

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### **Priority under 35 U.S.C. § 119**

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:

1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### **Attachment(s)**

1) Notice of References Cited (PTO-892)

2) Notice of Draftperson's Patent Drawing Review (PTO-948)

3) Information Disclosure Statement(s) (PTO/SB/08)  
 Paper No(s)/Mail Date \_\_\_\_\_

4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date \_\_\_\_\_

5) Notice of Informal Patent Application

6) Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 1, 2008 has been entered.

2. Claims 1-7, 9-17, 19-28, 30-38, 40-49, 51-59 and 61-65 were previously pending. Applicants amended claims 1, 2, 10-12, 24, 31-33, 45 and 52-54 and cancelled claims 9, 30 and 51. Claims 1-7, 10-17, 19-28, 31-38, 40-49, 52-59 and 61-65 are pending and will be examined.

3. Applicants' claim cancellations overcame the previously presented rejections for claim 9, 30 and 51. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" section below.

4. This office action contains new grounds for rejection.

### ***Response to Arguments***

5. Applicant's arguments filed December 1, 2008 have been fully considered but they are not persuasive.

Regarding the rejection of claims 1-7, 9-16, 19-28, 30-37, 40-49, 51-58 and 61-65 under 35 U.S.C. 103(a) over Fairman, and the rejection of claims 17, 38 and 59 under 35 U.S.C. 103(a) over Fairman and Hanak et al., Applicants argue the following:

Neither Fairman nor Hanak et al. teach or suggest the newly added limitation "wherein the hypertonic, high salt reagent comprises salt in an amount effective to precipitate proteins out of the lysate".

However, this limitation does not require that the high salt reagent actually precipitates the proteins (and the question is, all proteins or only some of them?) out of solution, but that the amount of salt it contains is effective in doing so. As no specific conditions are required by the claims, the hypertonic solution of Fairman under the conditions used by Fairman would be effective in precipitating some of the proteins out of the lysate, as shown in the evidence references. Further, the claims require only that the hypertonic reagent in step (b) contain an amount of salt effective to precipitate proteins, but in step (c) the cell suspension is contacted with a lysis reagent, which might decrease the salt concentration in the lysis solution relative to the hypertonic suspension of step (b), so it is not clear whether the salt concentration of the high salt reagent effective in precipitating proteins should be the concentration before adding the lysis reagent or after mixing with the lysis reagent.

The rejections are maintained.

***Claim Interpretation***

6. Applicants defined the term "hypertonic solution" on page 10, second paragraph:

" The first reagent, referred to herein as a "hypertonic, high-salt reagent," is a hypertonic reagent that includes a high concentrations of salts such as sodium, ammonium, or potassium salts dissolved in water. A hypertonic solution is a solution having a higher osmotic pressure than that found within a biological entity such as a cell or tissue."
7. Applicants did not define the term "salt in an amount effective to precipitate proteins out of the lysate", therefore it is interpreted as any salt concentration consistent with the term "hypertonic solution".

***Claim Rejections - 35 USC § 112, first paragraph, best mode***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-7, 10-17, 19-28, 31-38, 40-49, 52-59 and 61-65 are rejected under 35 U.S.C. 112, first paragraph, because the best mode contemplated by the inventor has not been disclosed.

Evidence of concealment of the best mode is based upon the fact that no compositions of reagents used in the example presented were provided or seem to be available. Specifically, the only example provided, Example 1 on pages 17-21, discloses reagents from a Puregene® kit, the compositions of which were not disclosed.

***Claim Rejections - 35 USC § 112, written description***

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-7, 10-17, 19-28, 31-38, 40-49, 52-59 and 61-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common

attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

The claims are broadly drawn to a method of isolating a DNA from a biological sample by

(a) contacting the biological material comprising DNA with a hypertonic, high salt reagent so as to form a suspension of the biological material comprising DNA;  
(b) contacting the suspension of step (a) with a lysis reagent to form a lysate comprising DNA and non-DNA biological components released from the biological material, wherein the hypertonic high salt reagent in step (a) comprises salt in an amount effective to precipitate proteins out of the lysate; and

(c) physically separating the DNA from the non-DNA biological components in the lysate of step (c) to yield isolated DNA.

The claims encompass all possible DNA samples, including bacteria, yeast, plant samples, soft tissue samples, bone samples, biological fluids, etc. For each one of these sample types different lysis buffers and lysis conditions are usually used, and the protocol used varies with the final method in which the DNA will be used, i.e., the purity of DNA required. Therefore, there are thousands of different conditions, the most commonly used of which contain for example, lysozyme, proteinase K, various types of cationic or anionic detergents, sugars (sucrose, sorbitol, etc.) and all possible combinations of these components in different buffers and concentrations. The term "salt" means any compound obtained by reacting an acid with a base, therefore, there are literally billions of such compounds encompassed by the claims. Taken together, the claims encompass billions of different experimental conditions possible in the case of DNA isolation from different types of cells.

Applicants provided a single example of isolating DNA from white blood cells using a set of reagents with undisclosed compositions.

Therefore Applicants were not in possession of the claimed subject matter.

***Claim Rejections - 35 USC § 112***

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 1-7, 10-17, 19-28, 31-38, 40-49, 52-59 and 61-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

**The nature of the invention and breadth of claims**

The claims are broadly drawn to a method of isolating a DNA from a biological sample by contacting the biological material comprising DNA with a hypertonic, high salt reagent so as to form a suspension of the biological material comprising DNA; contacting the suspension of

with a lysis reagent to form a lysate comprising DNA and non-DNA biological components released from the biological material, wherein the hypertonic high salt reagent comprises salt in an amount effective to precipitate proteins out of the lysate and physically separating the DNA from the non-DNA biological components in the lysate to yield isolated DNA. However, as will be further discussed, there is no support in the specification and prior art for the claimed methods. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has a single working example of isolation of DNA from white blood cells starting from the whole blood, using Puregene® kit reagents, the compositions of which were not disclosed. There are no examples of DNA purification from any other type of cells.

Guidance in the Specification.

The specification provides no evidence that the claimed method would work for all possible types of cells and DNA lysis conditions. The claims encompass all possible DNA samples, including bacteria, yeast, plant samples, soft tissue samples, bone samples, biological fluids, etc. For each one of these sample types different lysis buffers and lysis conditions are usually used, and the protocol used varies with the final method in which the DNA will be used, i.e., the purity of DNA required. Therefore, there are thousands of different conditions, the most commonly used of which contain for example, lysozyme, proteinase K, various types of cationic or anionic detergents, sugars (sucrose, sorbitol, etc.) and all possible combinations of these components in different buffers and concentrations. The term "salt" means any compound obtained by reacting an acid with a base, therefore, there are literally billions of such compounds encompassed by the claims.

Therefore, the salt to be used and the amount to be used will differ from sample to sample and from extraction protocol to extraction protocol, thus the guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

The unpredictability of the art and the state of the prior art

The claims are drawn to providing a hypertonic reagent to provide a suspension of a biological material followed by addition of a lysis solution, and the hypertonic solutions is required to be effective in precipitating proteins out of the lysate. However, the claims do not specify whether all of the proteins or just some of them are to be precipitated. Further, there are millions possible lysis buffers and salt solutions. As evidenced in the references cited below, protein solubility and conditions under which proteins precipitate depend on the composition of protein solution, protein properties, such as charge and overall stability, pH of the solution, presence of detergents, etc.

Moskaitis et al. (Neurochemical Res., vol. 11, pp. 299-315, 1986) teaches conditions for protein precipitation in solutions with SDS (Abstract). They examined proteins with overall positive and negative charges at neutral pH at a range of SDS concentrations and pH at 20° C (page 301, 302; Fig. 1-5, page 306, 307). Even though some of the proteins precipitated out of solution at a pH close to their pI values, some did not (see Fig. 1-5 and Table I; page 302, last paragraph; page 306, first paragraph).

Shih et al. (Biotechnol. Bioengin., vol. 40, pp. 1155-1164, 1992) investigated precipitation of proteins in solutions with different sodium salts at varying pH and temperatures (Abstract). The "salting-out constant" is characteristic for a given protein and salt (see page 1155, second and third

paragraph; Fig. 1). The salting-out constant for lysozyme was found to be slightly dependent on pH and strongly dependent on the type of salt (Table I). It was determined further that for some proteins (chymotrypsin, BSA) solubility depends on the initial concentration of the protein in solution, whereas for lysozyme it did not (Fig. 6-8).

In conclusion, the solubility of individual proteins in pure solutions cannot be predicted from the physicochemical characteristic of the proteins, but has to be experimentally determined. The situation becomes even more complicated in solutions with two or more proteins. Coen et al. (Biotechnol. Bioeng., vol. 53, pp. 567-574, 1997) examined solubility of proteins in mixtures of two proteins which either interact with each other (lysozyme and ovalbumin) or not (lysozyme-chymotrypsin) (Abstract) as a function of pH and salt concentration in ammonium-sulfate solutions. They determined that whereas in the case of the two non-interacting proteins their solubility was not affected by the presence of the second protein, for the two interacting proteins it was (Fig. 5, Fig. 9; page 572, first and second paragraph).

Therefore, since the solution of lysed cells contains thousands of different proteins with different charges and degrees of hydrophobicity, different structures and molecular weights, as well as all of the other cellular components like lipids, nucleic acids, sugars, etc., it is not possible to predict a priori for a given lysis solutions whether and to what degree the proteins will be precipitated out of such a system.

#### Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this method to DNA isolation from any type of biological sample under any lysis condition, including the influence of each of the lysis solution component, pH, temperature, and a type of salt used, for example. This would require years

of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the precipitation of proteins out of solution depend upon numerous known and unknown parameters such as the solution composition, pH, temperature, protein concentrations and composition, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

*Claim Rejections - 35 USC § 112, second paragraph*

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 1-7, 10-17, 19-28, 31-38, 40-49, 52-59 and 61-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-7, 10-17 and 19-23 are indefinite in claims 1 and 2. Claims 1 and 2 are indefinite over the recitation of "wherinc the hypertonic, high salt reagent ... comprises salt in an amount effective to precipitate proteins out of the lysate". It is not clear what the term "effective to

precipitate proteins out of a lysate" means. Does it mean an amount of salt which precipitates some of the proteins or all of them? Further, does the term "effective amount" mean an amount contained in the high salt reagent or in the mixture of the high salt reagent with the lysis reagent?

B) Claims 24-28, 31-38 and 40-44 are indefinite in claim 24. Claim 24 is indefinite over the recitation of "wherein the hypertonic, high salt reagent ... comprises salt in an amount effective to precipitate proteins out of the lysate". It is not clear what the term "effective to precipitate proteins out of a lysate" means. Does it mean an amount of salt which precipitates some of the proteins or all of them? Further, does the term "effective amount" mean an amount contained in the high salt reagent or in the mixture of the high salt reagent with the lysis reagent?

C) Claims 45-49, 52-59 and 61-65 are indefinite in claim 45. Claim 45 is indefinite over the recitation of "wherein the hypertonic, high salt reagent ... comprises salt in an amount effective to precipitate proteins out of the lysate". It is not clear what the term "effective to precipitate proteins out of a lysate" means. Does it mean an amount of salt which precipitates some of the proteins or all of them? Further, does the term "effective amount" mean an amount contained in the high salt reagent or in the mixture of the high salt reagent with the lysis reagent?

D) Claims 11 and 12 recite the limitation "the concentration of the salt" in lines 1/2. There is insufficient antecedent basis for this limitation in the claim. Neither claim 1 nor claim 2, from which these claims depend, refer to salt concentration. It is further not clear whether the salt concentration refers to the concentration in the high salt reagent or in the mixture of the high salt reagent with the lysis buffer.

E) Claim 16 recites the limitation "the concentration of the ionic detergent" in lines 1/2. There is insufficient antecedent basis for this limitation in the claim. Neither claim 14 nor claims 1 and 2, from which this claim depends, refer to detergent concentration.

F) Claims 32 and 33 recite the limitation "the concentration of the salt" in lines 1/2. There is insufficient antecedent basis for this limitation in the claim. Claim 24, from which these claims depend, does not refer to salt concentration. It is further not clear whether the salt concentration refers to the concentration in the high salt reagent or in the mixture of the high salt reagent with the lysis buffer.

G) Claim 37 recites the limitation "the concentration of the ionic detergent" in lines 1/2. There is insufficient antecedent basis for this limitation in the claim. Neither claim 24 nor claim 35, from which this claim depends, refer to detergent concentration.

H) Claims 53 and 54 recite the limitation "the concentration of the salt" in lines 1/2. There is insufficient antecedent basis for this limitation in the claim. Claim 45, from which these claims depend, does not refer to salt concentration. It is further not clear whether the salt concentration refers to the concentration in the high salt reagent or in the mixture of the high salt reagent with the lysis buffer.

I) Claim 58 recites the limitation "the concentration of the ionic detergent" in lines 1/2. There is insufficient antecedent basis for this limitation in the claim. Neither claim 45 nor claim 56, from which this claim depends, refer to detergent concentration.

***Claim Rejections - 35 USC § 103***

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. Claims 1-3, 6, 7, 10-17, 19-25, 27, 28, 31-38, 40-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Laitinen et al. (Biotechniques, vol. 17, pp. 316, 318, 320-322, 1994).

A) Claims 1, 2 and 24 will be considered together in claim 1, since it is a species of claims 2 and 24.

Regarding claims 1, 2 and 24, Laitinen et al. teach a method of isolating DNA from a biological sample comprising red and white blood cells, the method comprising the following sequential steps:

(a) separating the biological material comprising DNA from the remainder of the biological sample (Laitinen et al. teach separating nucleic from the remainder of the cells (page 316, sixth paragraph).);

(b) contacting the separated biological material comprising DNA of step (a) with a hypertonic, high salt reagent so as to form a suspension of said biological material containing DNA (page 316, sixth paragraph, where the nuclei are contacted with a lysis buffer and 5 M NaCl (=hypertonic salt reagent));

(c) contacting the suspension of step (b) with a lysis reagent so as to lyse the biological material containing DNA to form a lysate comprising DNA and non-DNA biological components released from the biological material, wherein the said hypertonic, high-salt reagent in step (b) comprises salt in an amount effective to precipitate proteins out of the lysate (page 316, sixth paragraph, where the nuclei are contacted with a lysis buffer and 5 M NaCl (=hypertonic salt reagent). Since the final salt concentration is 1.2 M, it is effective in precipitating proteins out of the lysate.); and

(d) separating the DNA from non-DNA biological components in the lysate to yield isolated DNA (page 316, sixth paragraph).

Regarding claims 3 and 25, Laitinen et al. teach vertebrate tissues, blood cells and bacterial cells (page 316, fourth paragraph).

Regarding claims 6 and 27, Laitinen et al. teach buffy coats (page 316, fourth paragraph). Since buffy coats are obtained from whole blood, Laitinen et al. inherently teach whole blood.

Regarding claims 7 and 28, Laitinen et al. teach purifying DNA from the rest of the cell, which contain proteins, lipids, RNA and carbohydrates (page 316, sixth paragraph).

Regarding claims 10 and 31, Laitinen et al. teach NaCl (page 316, sixth paragraph).

Regarding claims 11, 12, 32 and 33, Laitinen et al. teach NaCl solution with 5 M concentration (page 316, sixth paragraph).

Regarding claims 13-15 and 34-36, Laitinen et al. teach SDS (page 316, sixth paragraph).

Regarding claims 16 and 37, Laitinen et al. teach SDS concentration of 1% (page 316, sixth paragraph).

Regarding claims 17 and 38, Laitinen et al. teach RNase (page 316, sixth paragraph).

Regarding claims 19, 20, 40 and 41, Laitinen et al. teach vortexing the samples and centrifuging the lysate (page 316, sixth paragraph).

Regarding claims 21 and 42, Laitinen et al. teach precipitating the DNA with alcohol (page 316, sixth paragraph).

Regarding claims 22 and 43, Laitinen et al. teach washing the DNA pellets (page 318, first paragraph).

Regarding claims 23 and 44, Laitinen et al. teach treating DNA with a hydration reagent (page 316, sixth paragraph).

B) Laitinen et al. do not teach contacting the nucleic first with the high salt reagent.

However, the final result of step c), i.e., a mixture of the lysis reagent and a high salt reagent is achieved regardless of the order of addition of these two reagents. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to have reversed the steps of adding a high-salt solution before cell lysis. As stated in several Court decisions, changing the order of steps is *prima facie* obvious (see MPEP 2144.04.IV.C):

*Ex parte Rubin*, 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to render *prima facie* obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is *prima facie* obvious.).

18. Claims 1-7, 10-16, 19-28, 31-37, 40-49, 52-58 and 61-65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fairman (US 2002/0068280 A1; cited in a previous office action) as evidenced by Shih et al. (Biotechnol. Bioeng., vol. 40, pp. 1155-1164, 1992) and Moskaitis et al. (Neurochem. Res., vol. 11, pp. 299-315, 1986).

A) Claims 1, 2, 24 and 45 will be considered together in claim 45, since it is a species of claims 1, 2 and 24.

Regarding claims 1, 2, 24 and 45, Fairman teaches a method of isolating DNA from a biological sample comprising red and white blood cells, the method comprising the following sequential steps:

- (a) contacting the biological sample with a red blood lysis reagent to lyse the red blood cells (Fig. 1, step 120; page 1, [0010]; page 2, [0022]; page 3, [0027], [0028]);
- (b) separating the white blood cells from the lysed red blood cells (Fig. 1, step 130; page 2, [0022]; page 3, [0029]);
- (c) contacting the white blood cells with a hypertonic, high-salt reagent to suspend the white blood cells in a solution of said hypertonic, high-salt reagent (Fig. 1, step 130; page 2, [0022]; page 3, [0026], [0030]; since the second solution contains salt concentration of about 200-300 mM, it is a hypertonic solution. As evidenced by Shih et al., protein precipitation depends both on ionic strength of solution and pH, therefore, 200-300 mM salt concentration would be effective in precipitating some of the proteins from the lysate, especially in the presence of SDS, as evidenced by Moskaitis et al.);
- (d) subsequently contacting the white blood cells of step (c) with a lysis reagent so as to lyse the biological material containing DNA to form a lysate containing DNA and non-DNA cellular material (Fig. 1, step 140; page 2, [0022]; page 3, [0031]) and
- (e) separating the DNA from non-DNA cellular material of the lysate to yield isolated DNA (Fig. 1, steps 150, 160; page 2, [0022]; page 4, [0034]-[0040]; page 5, [0041]).

Regarding claims 3, 6, 25, 27, 46 and 48, Fairman teaches whole blood (page 2, [0022]).

Regarding claim 4, Fairman teaches whole blood (page 2, [0022]), therefore they inherently teach samples containing viruses.

Regarding claims 5, 26 and 47, Fairman teaches bone marrow (page 3, [0024]).

Regarding claims 7, 28 and 49, Fairman teaches separating the DNA from proteins (page 4, [0035]).

Regarding claims 13-16, 34-37 and 55-58, Fairman teaches using 0.1% w/v SDS in the lysis solution (page 2, [0022]).

Regarding claims 10-12, 31-33 and 52-54, Fairman teaches ammonium salt solutions with concentration of about 0.2-0.3 M (page 3, [0026]) and using 5 M solution of ammonium acetate to precipitate proteins (page 4, [0035]).

Regarding claims 19, 20, 40, 41, 61 and 62, Fairman teaches removal of the protein precipitate by centrifugation (page 4, [0037]).

Regarding claims 21, 22, 42, 43, 63 and 64, Fairman teaches precipitation of DNA with alcohol and centrifugation (page 5, [0041]), i.e. they teach precipitation and washing of the DNA.

Regarding claims 23, 44 and 65, Fairman teaches using the DNA in a PCR reaction, i.e. rehydrating the DNA (page 5, [0040]).

B) Fairman does not teach adding the high-salt solution which precipitates the DNA before lysing the cells.

However, it would have been *prima facie* obvious to one of ordinary skill in the art to have reversed the steps of adding a high-salt solution before cell lysis. As stated in several Court decisions, changing the order of steps is *prima facie* obvious (see MPEP 2144.04.IV.C):

*Ex parte Rubin*, 128 USPQ 440 (Bd. App. 1959) (Prior art reference disclosing a process of making a laminated sheet wherein a base sheet is first coated with a metallic film and thereafter impregnated with a thermosetting material was held to

render *prima facie* obvious claims directed to a process of making a laminated sheet by reversing the order of the prior art process steps.). See also *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) (selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results); *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (Selection of any order of mixing ingredients is *prima facie* obvious.).

19. Claims 17, 38 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fairman (US 2002/0068280 A1; cited in a previous office action) and Hanak et al. (U.S. Patent No. 6,780,632 B1).

A) The teachings of Fairman et al. are presented above. The reference does not teach using RNase in the purification protocol.

B) Hanak et al. teach preparing RNA-free DNA using RNase (Abstract; col. 2, lines 30-35; col. 35, lines 46-67; col. 36; col. 37; col. 38, lines 1-44).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used RNase of Hanak et al. in the DNA preparation method of Fairman. The motivation to do so, provided by Hanak et al., is that RNA is a major contaminant of preparations of genomic and plasmid DNA from cell lysates (col. 1, lines 36-50).

20. No claims are allowed.

### ***Conclusion***

21. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Schneider, U.S. Patent No. 5,596,092 A (issued January 1997).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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